2013-1306

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0805, Judge Christopher J. Burke.

CORRECTED REPLY BRIEF FOR PLAINTIFF-APPELLANT BRISTOL-MYERS SQUIBB COMPANY

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September 5, 2013

CERTIFICATE OF INTEREST

Counsel for Bristol-Myers Squibb Company certifies as follows:

1. The full name of every party or amicus represented by us is:

Bristol-Myers Squibb Company

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by us are:

None.

4. The names of all law firms and the partners or associates that appeared for the parties represented by us in the trial court, or are expected to appear in this Court, are:

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INTRODUCTION

BMS does not "propose[] a revolution in obviousness law," as Teva contends (Br. 21). Rather, it is the district court's decision that significantly deviated from precedent. The court concluded that the new chemical compound entecavir was obvious over a toxic prior art compound, despite finding several unexpected therapeutic properties that make entecavir a significant advance in an unpredictable field. The court reached that unprecedented result through an analysis that not only was hindsight-driven, but also ignored the court's own factual findings concerning several objective indicia of nonobviousness. Those errors of law pervade the court's analysis and require reversal.

Teva has identified no other case in which a new chemical compound found to possess unexpected therapeutic properties was held obvious, let alone a case such as this where those properties make entecavir the most potent treatment for hepatitis B ever discovered. Although Teva quibbles with the applicable doctrinal framework, it does not matter whether entecavir's extraordinary unexpected properties are viewed as preventing an initial finding of a reasonable expectation of success or the ultimate conclusion of obviousness. Either way, the district court's decision is a striking departure from established law.

The district court's six-step analysis for selecting and modifying 2'-CDG was also infected with legally erroneous hindsight. Using the inventors' own

discovery as a roadmap, the court impermissibly relied on the structure of *the patented invention* to inform the selection of 2'-CDG as a lead compound. The court then disregarded the teachings that would have led away from entecavir and dismissed the unpredictable choices that an ordinarily skilled artisan would have faced in a field where even seemingly small modifications can dramatically alter the safety and efficacy of the resulting compound. Although Teva stresses the length of the district court's opinion (Br. 20), the complexity of the court's path to obviousness is a symptom of the problem, not a basis for deference.

The objective indicia further reinforce the nonobviousness of BMS's invention. While Teva attempts to downplay their significance, the district court's findings of unexpected results, commercial success, and long-felt but unmet need provide a critical "guard[] against the use of hindsight." *Apple Inc. v. ITC*, ___ F.3d ___, 2013 WL 4007535, at *7 (Fed. Cir. Aug. 7, 2013). The court improperly discounted its findings of these powerful objective indicia based on multiple errors of law. When those errors are corrected and entecavir is properly "[v]iewed through the lens of the objective indicia, as opposed to the hindsight lens used by the [district court]," BMS's invention was clearly nonobvious. *Leo Pharm. Prods., Ltd. v. Rea*, ___ F.3d ___, 2013 WL 4054937, at *12 (Fed. Cir. Aug. 12, 2013).

ARGUMENT

I. THE DISTRICT COURT'S FINDING OF A REASONABLE EXPECTATION OF SUCCESS WAS LEGALLY ERRONEOUS AND CONFLICTS WITH ITS FINDING OF UNEXPECTED RESULTS.

The district court's finding of a reasonable expectation of success was based on the conclusion that an ordinarily skilled artisan "could have reasonably expected" entecavir to have "similar properties to 2'-CDG, including antiherpetic activity." A128. But that was not the success that BMS achieved with entecavir in a field where numerous compounds had strong activity yet proved unsuitable as pharmaceuticals. *E.g.*, A1208(821:6-16) (lobucavir); A1256(1011:3-1012:8) (fialuridine); A1341(1348:20-1349:2) (clevudine). Rather, BMS's success "was finding a compound that had high activity, few side effects, and lacked toxicity." *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000). By focusing solely on antiviral activity, the court measured success against the wrong standard.

Moreover, the district court's assumption about "similar properties" cannot be squared with its determination that entecavir and 2'-CDG, in fact, have vastly different properties. Although entecavir is much less active against herpes than 2'-CDG (*see* A16(¶41); A103), entecavir unexpectedly has "'extraordinary potency against' the hepatitis B virus" (A150 (quoting A1262(1036:2-8))). Indeed, it is the *most potent drug gram-for-gram ever discovered for treating hepatitis B.*

A48-49(¶¶133-134); A150. Entecavir also has "a very high genetic barrier to resistance," both because of its potency and because it inhibits replication of the hepatitis B virus at three independent steps. A49(¶¶135, 137). And entecavir is "a very safe and effective drug" that has "a large therapeutic window" between "the dose the effectively treats the hepatitis B virus" and "the dose that displays toxicity." A50-51(¶140). In contrast, researchers "never found a dose [of 2'-CDG] that wasn't toxic" in the leading animal model for studying hepatitis B (A1255(1010:5-6)), and 2'-CDG therefore has never been used in humans (A1255(1010:12-17)).

These unexpected properties are not, as Teva alleges, merely "a modest difference of degree over the prior art." Br. 33. They are profound differences in kind that separate a deadly compound with no therapeutic use from a life-saving new drug. Entecavir's unexpected therapeutic properties thus powerfully refute the district court's conclusion that entecavir would have been obvious. *See, e.g.*, *In re Chupp*, 816 F.2d 643, 647 (Fed. Cir. 1987) (claimed compound nonobvious due to its unexpectedly superior activity); *In re Ruschig*, 343 F.2d 965, 977 (C.C.P.A. 1965) (recognizing the "consistent line of decisions" holding new chemical compounds nonobvious based upon unexpectedly superior properties).

Contrary to Teva's repeated suggestion (Br. 1, 21-23, 26, 27), BMS is not advocating a per se rule against obviousness when there is any finding of

unexpected results. But because "a compound and all of its properties are inseparable" for purposes of assessing obviousness, *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963), it is legal error to reach a conclusion of obviousness where, as here, research in a highly unpredictable art yielded a new chemical entity with such unexpectedly superior therapeutic properties. *See, e.g.*, *In re Rousuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517-518 (Fed. Cir. 2012) (no reasonable expectation of success where compound possessed unexpected advantageous properties); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361-1362 (Fed. Cir. 2007) (same); *In re May*, 574 F.2d 1082, 1095 (C.C.P.A. 1978) (unexpected combination of properties in an unpredictable field "rebutted the presumed expectation that structurally similar compounds have similar properties").

Teva has not identified a single case in which this Court has held obvious a new chemical entity that possesses unexpected therapeutic properties. In *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), the claimed invention was the salt form of a known compound, not a new chemical entity. *Id.* at 1356. In any event, the patentee had "simply failed to prove that the results [we]re unexpected." *Id.* at 1371. While the Court noted in dicta that proof of unexpected results would not have changed the outcome, *id*. at 1372, the patentee itself had conceded that

those unexpected results would have "had no effect on the therapeutic effect of the active ingredient," *id*. at 1366.

Alcon Research, Ltd. v. Apotex Inc., 687 F.3d 1362 (Fed. Cir. 2012), involved *method* claims. *Id*. at 1364-1365. In addition, the evidence of unexpected results was particularly thin and peripheral to the claims at issue. *Id*. at 1368-1370 (noting that the prior art "disclose[d] every limitation of the[] claims except that the formulation can be used to treat eye allergies in humans" rather than guinea pigs, and it was known that "guinea pig models … are predictive of a compound's antihistaminic activity and its topical ocular availability in humans").

In *Allergan, Inc. v. Sandoz Inc.*, __ F.3d __, 2013 WL 1810852 (Fed. Cir. May 1, 2013), a formulation claim was held obvious notwithstanding the unexpected discovery that dosing twice-per-day overcame a known problem in the prior art because that unexpected property was tangential to the formulation claim, which did not include a dosing limitation. *Id.* at *2, *6. In contrast, the Court concluded that the method claims that expressly included the dosing limitation were nonobvious in light of this unexpected result. *Id.* at *7.

Teva suggests that entecavir's "[l]ater-discovered and unexpected properties" cannot preclude obviousness. Br. 22. This Court has made clear, however, that "every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness."

Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1307 (Fed. Cir. 2011); *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1384-1385 (Fed. Cir. 2004).

Teva attempts to sidestep the issue presented by BMS by arguing that "*Papesch* is irrelevant to the question of the requirements for a *prima facie* case." Br. 22 (quoting *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (en banc)). But *Dillon* reiterated the importance of considering all of a compound's properties when analyzing obviousness. *Dillon*, 919 F.2d at 697 ("*Papesch* indeed stated that a compound and all of its properties are inseparable and must be considered in the determination of obviousness. We heartily agree and intend not to retreat from *Papesch* one inch."). In any event, Teva's attempt to leverage *Dillon* into a bright line between the *prima facie* case and Teva's ultimate burden of persuasion on obviousness makes no difference in this case where the patent is presumed valid. "[A] fact finder[] must withhold judgment on an obviousness challenge until it considers all relevant evidence," *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012), and "the party challenging validity bears the burden of persuasion throughout the litigation," *id*. at 1078 n.5. It is thus immaterial whether entecavir's unexpected properties prevent an initial showing of a reasonable expectation of success or preclude an

ultimate conclusion of obviousness (*see infra* pp. 23-26). Either way, the claimed invention is nonobvious.

II. TEVA'S ARGUMENTS CONFIRM THAT THE DISTRICT COURT'S OBVIOUSNESS ANALYSIS WAS DRIVEN BY LEGALLY IMPERMISSIBLE HINDSIGHT.

Teva complains that "BMS's [six] 'steps'" tracing the district court's path to entecavir make the ordinarily skilled artisan's decisionmaking process "appear complicated." Br. 36. But those steps are precisely the theory that *Teva* presented at trial and the court adopted—and Teva is right that it *was* complicated. At each step, there were numerous reasonable or preferable alternatives with unpredictable results that a person of ordinary skill would have considered, and "[a]ny deviation … would have taught away from" entecavir. *Yamanouchi*, 231 F.3d at 1345. Only by relying on hindsight and other legal errors was the court able to find its way to entecavir.

A. The District Court's Lead Compound Analysis Improperly Relied On The Structure Of The Claimed Invention And Disregarded Reasonable Or Preferred Alternatives.

1. The court incorrectly relied on the structure of the claimed invention to select a lead compound.

The district court erred as a matter of law when it relied on the perceived structural similarity of 2'-CDG to the *claimed invention* to justify its selection of a lead compound. *See* BMS Br. 43-44. Teva concedes that the court considered structural similarity in selecting a lead compound, but attempts to excuse that error

because "structural similarity is a factor that the court was required to examine in the obviousness inquiry." Br. 42. Teva's argument misses the point. While structural similarity may be relevant for other purposes, "structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012). "Were it otherwise, the analysis would impermissibly rely upon *ex post* reasoning." *Id.*

Teva's attempt to rely on Dr. Schneller's testimony to establish a motivation to select 2'-CDG as a lead compound also fails. *See* Br. 41-42. When asked whether 2'-CDG would have been a possible lead compound, Dr. Schneller stated that it was at most one of the "hundreds" of compounds that might be "on the list." A1282(1111:7-23). Even then, Dr. Schneller made clear that he "would not put it high on the list" because there were other far more promising compounds known in the art. A1282(1113:13-24). That is hardly a ringing endorsement of 2'-CDG, let alone the damaging concession that Teva makes it out to be.

2. The record discloses numerous alternatives that a person of ordinary skill would have considered or preferred when selecting a lead compound.

The district court also erred by failing to give adequate consideration to the numerous alternatives to 2'-CDG that would have been considered or preferred as lead compounds. Teva defends the court's focus on carbocyclics by repeating its

statements that the field of carbocyclics was "fertile" with "growing interest." Br. 38. But Teva's own arguments confirm that a person of ordinary skill would have preferred acyclics or furanosides as lead compounds, or at least considered them as reasonable alternatives. For example, Teva points to three compounds to show that "[b]y 1990, the knowledge of nucleoside analogs had advanced to the point that researchers knew what was reasonably likely to produce an effective antiviral compound." Br. 25. None of those compounds is a carbocyclic: two are acyclics (adefovir and tenofovir) and the other is a furanoside (lamuvidine). A9002; A9013; A9014; *see* A1041(158:11-160:1) (explaining differences between three classes of nucleoside analogs); A1195(768:20-769:14); A9003. Teva concedes, moreover, that although there were FDA-approved acyclics and furanosides, "the FDA had yet to approve a carbocyclic." Br. 39.[1]

Nor is Teva correct to dismiss as attorney argument the statements *in the prior art* disparaging the antiviral activity of carbocyclics. Br. 39-40. The cited reference (A2091) was relied on by the district court, and it is error to consider "references in less than their entireties" by "disregarding disclosures in the references that diverge from and teach away from the invention at hand." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983).

[1] Even today, entecavir remains the *only* carbocyclic that is an FDA-approved hepatitis B treatment.

Together with testimony that an ordinarily skilled artisan would have selected an acyclic or furanoside instead (*e.g.*, A1282-1283(1112:4-1115:15)), this record evidence confirms that acyclics and furanosides were at least as promising as, if not more promising than, carbocyclics.

In addition, other references disclosed carbocyclics having far greater antiviral activity than 2'-CDG. *See* BMS Br. 44 (citing A2091, A2149). Teva does not deny, for example, that the Montgomery article taught that another compound (C-DAPdR) had *twice the antiviral activity of 2'-CDG*. *See* A2149 (Fig. 4). Teva attempts to downplay this fact because C-DAPdR is a "prodrug" form of 2'-CDG (Br. 42), but that does not diminish C-DAPdR's potential as an alternative lead compound. Indeed, Teva's expert acknowledged that pharmaceuticals are sometimes administered as prodrugs, which can improve their pharmacology. A1049(190:16-191:1).[2]

Nor is Teva correct that 2'-CDG would have been an obvious choice for further research simply because it was being used by some researchers as a lead compound. Br. 41. If that were the test, there were numerous other compounds that researchers were pursuing as leads. *E.g.*, A19-20(¶56).

[2] A prodrug is a compound that converts into the drug inside the body. A1049(190:16-21).

None of this is to say that "the prior art must point to one and only one lead compound." Teva Br. 37. But it was error for the court to focus exclusively on 2'-CDG while failing to consider the many possible modifications flowing from the selection of other lead compounds. Had the court considered those alternatives, it never could have concluded that there were "a small, finite number of changes to try." A117; *see Takeda*, 492 F.3d at 1357-1359 (claimed invention not obvious to try where "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation").

B. The Prior Art Taught Numerous Alternative Modifications That Would Have Led Away From Entecavir.

1. The district court ignored the prior art teachings to modify the guanine base.

The district court found that, having selected 2'-CDG as a lead compound, a person of ordinary skill would have modified its carbocyclic ring rather than its guanine base. A113-115. That finding cannot be reconciled with the prior art underlying the court's analysis. Even the inventors of 2'-CDG were modifying its

guanine base and touting those changes as creating "[b]y far the most promising" antiviral compounds. A2148.[3]

Although the district court focused on modification to 2'-CDG's carbocyclic ring, Teva does not dispute that the prior art taught modifications to the base portion of nucleoside analogs resulting in *improved* antiviral activity. *See* BMS Br. 48-49 (citing A2012, A2148-2149). Teva instead attempts to avoid the prior art's teaching that base-modified compounds showed "potent activity" (A2012) by emphasizing contrary examples in the prior art. Br. 44-45. But that simply illustrates the unpredictability in this field, not that ordinarily skilled artisans would have *avoided* modifying 2'-CDG's base portion.

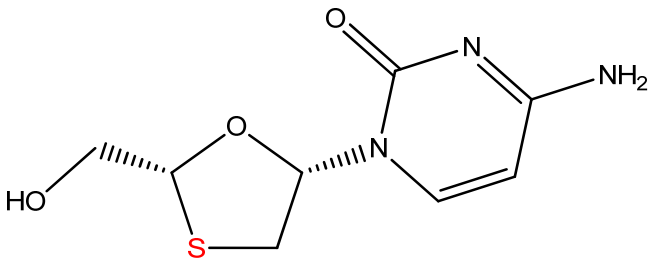
Moreover, contrary to the district court's determination that an ordinarily skilled artisan would have modified 2'-CDG's carbocyclic ring, the prior art discouraged significant modifications to that portion of the compound as "generally ineffective." A2130. Teva does not deny that teaching, but argues that it "would not have deterred a POSA from making a much simpler modification to the carbocylic ring." Br. 45. The addition of an exocyclic methylene, however, is a significant change to the structure of a carbocyclic ring—precisely what the prior

[3] Contrary to Teva's suggestion (Br. 43-44), Dr. Schneller did not testify that it would have been obvious to modify the carbocyclic ring. Dr. Schneller's testimony cited by Teva states only that a scientist would make "conservative changes" generally; it does not address whether those changes might be to the guanine base, the carbocyclic ring, or both. A1291; A1303.

art said should be avoided. A2130. As Dr. Schneller explained and Teva did not dispute, the addition of a methylene at the 6'-postion substantially alters the molecule's shape, which may prevent its biological target from recognizing the resulting compound. A1273-1274(1079:9-1086:17).

2. Teva concedes that there were multiple locations on the carbocyclic ring that an ordinarily skilled artisan would have been motivated to modify.

Although the district court determined that a person of ordinary skill would have focused exclusively on modifying the 2'- and 6'-positions of 2'-CDG, Teva's own arguments show that is not true. For example, lamivudine—one of the three compounds that Teva touts as evidence that "[b]y 1990 … researchers knew what was reasonably likely to produce an effective antiviral compound" (Br. 25)—contains a sulfur (shown in red) substituted at the *3'-position*:



lamivudine

See A1283(1117:13-23); A9002. Only in hindsight could the court choose to ignore that alternative leading away from entecavir.

As between the 2'- and 6'-positions, the "art and testimony" (Br. 46) that supposedly pointed to the 6'-position all relates to a single reference (Madhavan). Teva does not address other references teaching desirable modifications to the 2'-position—including changes that resulted in "unprecedented biological activity" (A2091). Instead, Teva argues that a person of ordinary skill did not need to choose between modifying the 2'- and 6'-positions to find the invention obvious to try. Br. 46. But Teva's argument demonstrates only the availability of alternative positions to modify, not that an ordinarily skilled artisan would have been motivated to make the changes leading to entecavir.

3. Teva does not dispute that scientists were modifying nucleoside analogs with numerous elements.

Contrary to Teva's suggestion (Br. 47), there was no "agreement" between the experts that an ordinarily skilled artisan would have considered modifying 2'-CDG with a carbon group to be the "most obvious" choice. Dr. Schneller simply confirmed that carbon "sticks out" as the element likely to produce the most conservative changes among those in the first row of the periodic table. A1304-1305(1200:1-1203:24). He never testified that an ordinarily skilled artisan would have been *limited* to the first row of the periodic table and, in fact, he identified numerous elements other than carbon that scientists had successfully used to modify nucleoside analogs. A1283(1116:16-1117:23) (discussing FDA-approved antiviral nucleoside analogs containing iodine-, sulfur-, and nitrogen-based

modifications); A9001; A9002. Teva's expert, Dr. Heathcock, similarly identified fluorine as an element that an ordinarily skilled artisan would have been equally likely to use as carbon. A1053(206:5-13). The experts thus agreed that carbon was *not* the only choice.

Although Teva tries to diminish the antiviral activity of the scores of prior art compounds modified using elements other than carbon (Br. 47; *see* BMS Br. 51-52), it ignores the praise for such compounds. A2130 (touting the "antiviral usefulness" of compounds containing nitrogen- and iodine-based substitutions). Moreover, Teva's arguments confirm that a person of ordinary skill would have been drawn to elements beyond the first row of the periodic table. As noted above, Teva highlights lamivudine (Br. 25), which involved a *sulfur* substitution. *See supra* p. 14.

4. The addition of 6'-methylene was far from routine and known to be associated with increased toxicity.

The district court's determination that it would have been obvious to add a methylene group at the 6'-position was also the product of hindsight. Teva does not dispute that, of the dozens of references the court considered, only the Madhavan article—and only one toxic compound described in that article (compound 30)—disclosed the addition of a methylene at the 6'-position. That is not the type of routine modification that an ordinarily skilled artisan might try. *See Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1355 (Fed. Cir. 2010) (no

motivation to modify where "few compounds" contained the specific modification); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009) (rejecting motivation to modify absent evidence that "the structural modification was routine").

Teva attempts to fill that gap by pointing to two other references (Takenuki and Ueda) teaching the addition of a methylene to a nucleoside analog. Br. 48-49. Teva ignores, however, that Takenuki and Ueda *led away from entecavir*. Both involved research with *furanosides*, not carbocyclics. A2008; A2025. Ueda taught modifications to the *base* with elements from *outside* the first row of the periodic table. A2025 (chlorine, bromine, and iodine). Neither showed the addition of a methylene to the 6'-position (as Teva admits (Br. 48)), and Takenuki taught modifications to the *4'-position* among others (A2008 (compound 2)). And, like Madhavan, neither discussed nucleoside analogs with a guanine base. A2008; A2025.

With respect to the Madhavan article, Teva selectively emphasizes the potency of compound 30 while attempting to downplay its toxicity. Br. 49. Compound 30, however, was not just a little more toxic than the others; it was toxic at concentrations more than *four times* lower than any other compound that Madhavan synthesized. A2003 (Tbl. I). Teva dismisses the relative toxicities as unsupported by expert testimony, but the authors of the article were explicit that

compound 30 was "*the most toxic*" and that compound 24 (which lacked an exocyclic methylene group) "was *nearly as active and much less toxic*." A2003 (emphases added). An ordinarily skilled artisan would not ignore Madhavan's explicit teachings, let alone make the counterintuitive choice of adding a methylene when Madhavan disclosed an alternative with similar activity and greatly reduced toxicity.

Teva also argues that a methylene group would have been a "more conservative choice" than a methyl group because it is smaller in size. Br. 48. Teva's expert conceded, however, that an ordinarily skilled artisan "certainly" would consider adding a methyl group, since it is only "a little bit bigger" than a methylene. A1053(208:12-209:1). There was no evidence that such a small difference in size or surface area would be the deciding factor in choosing how to modify a molecule. Even the Ueda reference that Teva now praises (Br. 49) taught examples of carbon-based substitutions that were significantly larger than a methyl group. *E.g.*, A2025. Moreover, Teva's suggestion that the addition of a methylene entails merely "adding a single carbon atom" (Br. 2) is overly simplistic. A methylene adds a double-bond, which significantly changes the molecule's overall structure and may prevent the resulting compound from being recognized by its biological target. A1273-1274(1079:9-1086:17); A1281(1106:3-23). The addition

of a 6'-methylene—taught only in a single prior art reference—simply was not the "conservative choice" that Teva now makes it out to be.

Nor did Dr. Schneller testify that adding a 6'-methylene was an obvious choice, as Teva suggests (Br. 48-51). Teva denies that Dr. Schneller's testimony that carbon is the "only" element that "sticks out" pertained to methyl substitutions. Br. 49-50. But that is exactly what Dr. Schneller said. *E.g.*, A1304(1201:11-12) ("That's what I said, but I said it's a methyl group, if I recall."). Dr. Schneller also testified at length about what a dramatic change the addition of a methylene would have on a molecule's structure. A1272-1274(1075:5-1083:9). Even if Teva were correct that "the easiest way to add a methyl group" is to start with a methylene substitution (Br. 48),[4] there is no reason why stopping at that intermediate step would have been a conservative change. Indeed, this Court has rejected that same argument before. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (concluding that it was not obvious to make the claimed invention by stopping at a chemical intermediate).

In addition, Teva's argument (Br. 50-51) that Dr. Schneller conceded that the toxicity of Madhavan 30 "might not dissuade" an ordinarily skilled artisan

[4] The Ueda reference that Teva relies upon taught adding a methyl group without going through a methylene intermediate. *E.g.*, A2019-2020 (describing the use of methyl-lithium and trimethylaluminum to add a methyl substitution).

from adding a methylene group ignores the context of his testimony. Dr. Schneller consistently emphasized the unpredictability of nucleoside analog research. A1270-1271(1069:4-1071:3); A1277(1096:17-1098:21); A1289(1140:2-1141:1). His testimony about Madhavan was no different. Because the field was unpredictable (and the Madhavan compounds had different enzymatic targets than 2'-CDG), Dr. Schneller testified that Madhavan "could have led" an ordinarily skilled artisan to include a 6'-methylene substitution—just as it could have led away from making such a change. A1312(1231:5-1232:17). Moreover, Dr. Schneller made clear that Madhavan "would certainly not suggest that one of ordinary skill in the art should make an *antiviral molecule* with a 6' exocyclic methylene group." A2185 (emphasis added); *see also* A1317(1250:16-1251:4) (testifying on redirect that "[t]here are toxicity problems" and "different enzyme targets" that would not have led an ordinarily skilled artisan to combine 2'-CDG with Madhavan).[5]

[5] Teva criticizes BMS for not disclosing 2'-CDG during prosecution. But as the district court found—and Teva does not challenge on appeal (Br. 7)—this omission was neither intentional nor inequitable. A170-171. The '244 patent claims dozens of compounds that bear no resemblance to 2'-CDG. A217-218. BMS disclosed the only prior art reference (Madhavan) that taught the most prominent feature shared by all compounds claimed in the patent—the exocyclic methylene group at the 6'-position. A1215(849:6-850:5). And contrary to Teva's suggestion (Br. 2, 24), the burden remains with Teva at all times to prove invalidity by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2249-2250 (2011) (holding that the clear and convincing standard does not "rise and fall with the facts of each case").

C. In Finding Entecavir Obvious To Try, The District Court Failed To Consider The Multiple Alternatives With Unpredictable Results At Each Step Of Its Analysis.

Teva's argument that entecavir would have been obvious to try merely repeats the district court's error. Rather than address *all* the decision points in the court's analysis, Teva focuses just on the final choices where it contends that there were only six possibilities. Br. 52. Teva ignores the preceding decision points and the countless combinations and permutations of choices that go with them. Those choices take this case far beyond the "finite," "small," or "easily traversed" number of possibilities that could support a conclusion of obviousness. *Cyclobenzaprine*, 676 F.3d at 1072; *see Leo Pharm.*, 2013 WL 4054937, at *9 (rejecting obvious to try argument in light of the "breadth" of choices and "numerous combinations" presented in the prior art); *Ortho-McNeil*, 520 F.3d at 1364 (concluding that a new compound was not obvious to try given all the decisions along the proposed path to the invention).

Moreover, contrary to Teva's suggestion (Br. 53), BMS does not contend that there must be "absolute predictability" to find the invention obvious to try. But here the art was highly unpredictable (BMS Br. 59), and both parties' experts agreed that seemingly small differences in chemical structure could have a significant impact on properties (*e.g.*, A1041(161:5-15); A1270-1271(1069:16-1071:14)). This case is therefore far removed from a situation where the invention

was merely one of "a finite number of identified, *predictable* solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (emphasis added); *see Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008) ("We agree that the obviousness of a selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in *KSR*.").

The fact that none of the scientists studying 2'-CDG made entecavir in the *six years* following 2'-CDG's disclosure in 1984 confirms that the claimed invention was not obvious to try. *See* BMS Br. 57-58; *Leo Pharm.*, 2013 WL 4054937, at *7 ("If these discoveries and advances were routine and relatively easy, the record would undoubtedly have shown that some ordinary artisan would have achieved this invention within months of [the prior art disclosures].").

III. THE OBJECTIVE CONSIDERATIONS OVERWHELMINGLY SUPPORT NONOBVIOUSNESS, BUT SEVERAL ERRORS OF LAW CAUSED THE COURT TO DISCOUNT THEM.

The district court found several objective indicia of entecavir's nonobviousness. Although Teva seeks to downplay their significance, this Court has repeatedly emphasized that objective evidence is "*part of* the whole obviousness analysis, not just an afterthought," *Leo Pharm.*, 2013 WL 4054937, at *11, and serves as a "powerful tool[] for courts faced with the difficult task of avoiding subconscious reliance on hindsight," *Mintz v. Dietz & Watson, Inc.*, 679

F.3d 1372, 1378 (Fed. Cir. 2012). Here, the court's findings of unexpected results, commercial success, and long-felt but unmet need demonstrate entecavir's nonobviousness and compel reversal.

A. The Objective Considerations Found By The District Court Are Powerful Evidence Of Nonobviousness.

1. The court improperly discounted its own finding of unexpected results based on an improper comparison to tenofovir and impermissible reliance on inventor expectations.

Entecavir does not just have "excellent activity" against hepatitis B (Teva Br. 56); the district court found that "[e]ntecavir is more potent *in vitro* than every other tested compound" and *in vivo* "is more potent than any of the hepatitis B drugs that were FDA-approved before it." A48(¶¶133-134). The court also found that entecavir is "a very safe and effective drug" (A50-51(¶140)) and has "a very high genetic barrier to resistance" (A49(¶137)). For example, "more than 70% of lamivudine patients" and "29-42% of adefovir patients" develop viral resistance within five years. A50(¶138). But only 1.2% of patients receiving entecavir as their first treatment for hepatitis B develop resistance after six years. A49(¶137). Although the court found these properties to be "unexpected" (A151), two legal errors prevented it from giving that finding the dispositive weight that it deserves.

First, the court discounted the evidence of unexpected results based on an improper comparison to tenofovir. Teva does not dispute that unexpected results

are measured against the *closest* prior art and that tenofovir was never offered as part of any prior art obviousness combination. Br. 57-58; *see also* BMS Br. 63. Nor does Teva deny that the court measured unexpected results, in part, by comparing entecavir to tenofovir. *See* A149. Teva argues instead that BMS "[i]nvited" the district court's error by mentioning tenofovir in the unexpected results section of its post-trial brief. Br. 57. BMS's argument, however, directly responded to the testimony of *Teva's* expert, Dr. Thio, who was the first to mention tenofovir and made it the centerpiece of her opinion on unexpected results, as well as Teva's pre- and post-trial arguments. A1117(461:16-22); A1118(464:2-13).

Second, the court impermissibly relied on *inventor* expectations to determine what one of *ordinary skill* would have expected. Teva repeats the same error when it argues that some degree of activity against hepatitis B and low toxicity "'could have been predicted at the time of entecavir's invention.'" Br. 56 (quoting A150). The finding that Teva quotes is based on the expectations of Dr. Zahler, one of the named inventors of BMS's patent. *See* A149-150 ("BMS expected …. This belief was based on Dr. Zahler's 'scientific judgment' …. Dr. Zahler was 'optimistic,' based on BMS's prior work …. [T]his testimony, coupled with the description in the patent's own specification, suggests that [activity against hepatitis B and low toxicity] could have been predicted at the time of entecavir's invention.").

Despite conceding that "[t]he district court used inventor testimony" and that the inventor's expectations are "not pertinent," Teva maintains that there was no error because the court used this inventor testimony "solely to 'illuminate[]'" the expectations of an ordinarily skilled artisan. Br. 58. This Court has made clear, however, that "'[i]nventors, as a class … possess something … which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees … would have known or would likely have done.'" *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) (quoting *Standard Oil Co. v. American Cyanamid Co*., 774 F.2d 448, 454 (Fed. Cir. 1985)). It was legal error for the court to rely on inventor expectations to establish the expectations of one of ordinary skill, and this error caused the court to discount its finding of unexpected properties.

Teva's remaining arguments do not diminish the force of these legal errors. Teva contends that some activity against hepatitis B could have been predicted based on 2'-CDG. Br. 56, 58. But there is no evidence that 2'-CDG shares entecavir's remarkable potency and barrier to resistance. Indeed, the striking contrast between these two compounds drives home just how unexpected entecavir's properties were. *See Yamanouchi*, 231 F.3d at 1345 ("The success of discovering [the new compound] … was finding a compound that had high activity, few side effects, and lacked toxicity.").

Teva also argues that entecavir's exceptional safety and its barrier to resistance would not have been unexpected because an ordinarily skilled artisan would not have known that 2'-CDG is toxic or that resistance to other drugs is a problem. Br. 56. But "evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date." *Genetics Inst.*, 655 F.3d at 1307. Ignorance regarding the correct baseline against which unexpected results should be measured is not a basis for discounting such evidence. *See id*.

2. Baraclude's commercial success demonstrates nonobviousness.

The district court found that "Baraclude has been commercially successful" (A135), "Baraclude was priced at a premium over its competitors" (A136), and "Baraclude's commercial success can primarily be attributed to its chemical properties" (A54-55(¶152)). From 2005 to 2011, Baraclude generated $3.8 billion in revenue from worldwide sales and $835 million in revenue from U.S. sales. A52(¶145). Baraclude "established itself as the number one drug in the market by early 2009" with a "peak market share of 36 percent" and maintained an "approximately 34 percent" market share in the face of new competition. A52-53(¶147). Indeed, Teva chose to copy Baraclude precisely because of its commercial success. A52(¶146).

Teva seeks to minimize Baraclude's undisputed commercial success by arguing that it could have been even more dynamic. Br. 55. But Baraclude's performance compares favorably to other products found to be successful. *See, e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1382 (Fed. Cir. 1986) ("substantial market impact" of diagnostic kits based on $14.5 million in sales over four years and a 25% market share). Moreover, "[t]here is no requirement that the invention be the only successful product in its market niche or the most successful." *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006), *aff'd sub nom. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). Indeed, when it comes to its own products, Teva has not hesitated to label smaller sales and market share over the same time period as "very successful." *See* No. 2:10-cv-5078 (D.N.J.), Dkt. 524-1 at 2, 25 ("Azilect® has been commercially very successful, generating over $1.7 billion in worldwide sales, $650 million in U.S. sales [over six years] and a 27% share of sales among Parkinson's disease treatments …."); *id.* at 11, 24 (Azilect approved in 2006, the year after Baraclude).

Baraclude has had billions of dollars in sales worldwide since its launch and holds a third of the market based on the remarkable properties of entecavir. This success rebuts Teva's hindsight-driven portrayal of entecavir as nothing more than an obvious result of ordinary skill.

3. Entecavir satisfied a long-felt but unmet need.

The district court found that "there was clearly a long-felt but unmet need for an effective hepatitis B treatment as of October 1990." A147-148. Approximately two billion people are infected with the virus, and 350 million people are infected with chronic hepatitis B. A58(¶161). Between 600,000 to one million people die from the disease each year, making it one of the top ten causes of death worldwide. *Id.* Yet, as of 1990, *not a single drug for treating hepatitis B had been approved by the FDA.* A60(¶169); *see also* A58(¶162) ("In 1990, the hepatitis B statistics were similar to current statistics.").

Teva concedes that "in 1990, there was a need for an effective drug to treat HBV," but argues that this need has since been met by three other nucleoside analogs. Br. 56. Teva's argument is not only unsupportable, but legally irrelevant. Courts "look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *Procter & Gamble*, 566 F.3d at 998. None of the nucleoside analogs mentioned by Teva was approved as of 1990. A61(¶172) (lamivudine approved in 1998); A62(¶174) (adefovir approved in 2002); A63(¶176), A65(¶179) (tenofovir approved for HIV in 2001 and hepatitis B in 2008).[6] And although the compounds may have been invented before entecavir,

[6] Even after approval, two of the drugs (lamivudine and adefovir) proved inadequate. Unlike with Baraclude, patients developed resistance to both drugs at an alarming rate, and neither is used as a first-line therapy. A61-62(¶¶173-174).

there is no evidence that in 1990 a person of ordinary skill would have considered the problem of developing a therapeutically effective treatment for hepatitis B to be solved. *See Procter & Gamble*, 566 F.3d at 998 (long-felt need remains unmet, despite competing inventions, where the competing inventions are not produced until after the claimed invention's filing date); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998) (same).

The lack of any therapeutically effective treatment for hepatitis B—let alone a treatment with the superior properties of entecavir—was not some esoteric problem. It was a matter of life and death for millions of people. Researchers thus had every incentive to search for a solution. Had entecavir actually been obvious to ordinarily skilled artisans at the time, as opposed to merely appearing obvious in hindsight to a court twenty-three years later, researchers would not have ignored such a solution. The fact that none independently discovered entecavir and no other treatment for hepatitis B had come to market provides compelling evidence that entecavir was not obvious.

B. The District Court's Analysis Of The Objective Considerations Was Legally Flawed.

The district court improperly discounted its own findings regarding unexpected results, commercial success, and long-felt but unmet need based on a fundamentally flawed approach to analyzing the objective considerations. Rather than consider the effect of its findings on the remainder of the court's analysis—

and, in particular, the profound impact of these unexpected results on its initial determination regarding a reasonable expectation of success—the court made an overall assessment that the objective considerations were "mixed" because, on the issues of copying, skepticism, and failure of others, it had "not found the evidence put forward by BMS to be particularly compelling." A152. The court then concluded that these "mixed" objective considerations "did not strongly persuade the Court as to entecavir's nonobviousness." A153.

That approach rested on the flawed assumption that the alleged *absence* of compelling evidence on some issues *negated* the court's findings that there were multiple indicia of nonobviousness. *See* BMS Br. 64. This Court has made clear that the "absence of objective evidence is a neutral factor." *Medtronic Inc. v. Intermedics, Inc.*, 799 F.2d 734, 739 n.13 (Fed. Cir. 1986); *see also Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1478 (Fed. Cir. 1998) (consideration of "long felt need and commercial success" could "only further support nonobviousness" because "the absence of objective evidence [of long felt need and commercial success] is a neutral factor" (quotation omitted)). Even a single objective factor—or even a single unexpectedly superior property—on its own can be dispositive. *See* BMS Br. 64 (citing cases).

Teva attempts to recast the district court's decision as an effort to give weight to objective considerations that affirmatively support obviousness. Br. 59.

But that is not what the court did: its findings on copying, skepticism, and failure of others were framed as a *rejection* of BMS's evidence, not as a finding that the evidence supported obviousness. *See* A134 ("Teva's choice to copy entecavir … does not amount to compelling evidence of nonobviousness …."); A140 ("In the absence of additional corroborating evidence," the "claim of skepticism is simply not enough to weigh in BMS's favor …."); A145 ("[T]he proffered evidence regarding 'failure of others' fails to persuasively demonstrate that entecavir was not obvious.").[7]

This perceived absence of evidence on some considerations simply cannot negate the compelling evidence of unexpected properties, commercial success, and long-felt but unmet need—all of which require reversal of the district court's decision. *See Leo Pharm.*, 2013 WL 4054937, at *11 (reversing obviousness determination where the same collection of objective indicia—unexpected results, commercial success, and long-felt but unmet need—were "the most probative evidence of nonobviousness … enabl[ing] the court to avert the trap of hindsight" (quotation omitted)).

CONCLUSION

The invalidity judgment should be reversed.

[7] The court's decision to count Teva's admission of copying *against* BMS confirms that the court improperly balanced the objective considerations.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing Corrected Reply Brief for Plaintiff-Appellant Bristol-Myers Squibb Company with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system this 5th day of September, 2013, and served a copy on counsel of record by the CM/ECF system and by electronic mail to the parties on the service list below.

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CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B)(ii).

1. Exclusive of the exempted portions of the brief, as provided in Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b), the brief contains 7,000 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2010 in 14 point Times New Roman font. As permitted by Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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